(Tim Frank, IRSF Chief Marketing & Development Officer):
Hello, welcome. My name is Tim Frank. I'm the Chief Marketing & Development Officer here at the International Rett Syndrome Foundation. Thanks for joining us today.

We are celebrating, as a community, a pretty monumental milestone. Just earlier this month, a little over a week ago trofinetide received the FDA's approval as the first-ever treatment for Rett Syndrome. So it's a humongous effort. It took so many people many years to get us to this place. And we are excited, and yet we are also eagerly awaiting kind of more information. Acadia Pharmaceuticals is the company that will be marketing the drug as DAYBUE in the United States. And the community has a lot of questions, so we want to answer some of those about the treatment and what comes next.

So, IRSF has put together a three-part Q & A series to start to answer your questions. We want to share what you need to know now and discuss the impact this treatment could have for you and your family, especially your loved one with Rett Syndrome.

Today in part one, I've asked Dr. Dominique Pichard, our Chief Science Officer here at the International Rett Syndrome Foundation, to come and talk to us a little bit more. Dominique is also a parent to a teenager with Rett Syndrome. I, myself am a parent to an almost teenager with Rett Syndrome. And she's going to share a little bit about the science behind DAYBUE, what we learned from the clinical trials, and discuss the specifics around the label and how to get this medication if you're interested, which has just recently been approved by the FDA.

Please remember that as we're sharing today, the thoughts and opinions discussed here in this video are not meant to be medical advice. We encourage you strongly to talk to your doctor about the individual advice that they would give you on DAYBUE and your child's treatment plan.

So Dr. Dominique Pichard, thanks for being here today. Tell me, how did you feel when you heard the news that the FDA had approved trofinetide?

(Dr. Dominique Pichard, IRSF Chief Science Officer):
That's a great way to start this off. There are so many words that come to mind, none of which really do justice to how I felt that Friday night when I was with my daughter who has Rett Syndrome when I finally got the news that trofinetide was approved. I was elated. This is a monumental milestone, as you said, for Rett Syndrome. There are so many days and moments that we talk about in Rett Syndrome. You know, I remember the day I asked my doctor, does she have Rett Syndrome, the diagnosis day. And now I have the trofinetide approval day that is stamped in my memory as one of the happiest moments for us as a family and hopefully for the larger community.

(TF) I'm not getting tired anytime soon of hearing people's reactions to this news. It is emotional, it is so encouraging to hear from one another, because it has, as you said, it's seared into our brains of these different days. And now there's finally a hopeful date seared into our brains as well.

Let's talk a little bit about trofinetide, which is now called DAYBUE, but we'll get into that. Tell me a little bit about what it is exactly and what we know about how it works. What do we know about how it works?

(DP) We're going to be a little bit technical here just because of the nature of that question. So trofinetide is a drug or a medication that is made to mimic a naturally occurring molecule in the brain,

and it is mimicking the amino-terminal peptide, something called IGF-1. So that was a whole lot of jargon. This amino-terminal peptide is called GPE. So you may hear IGF-1 and GPE as these terms. And the reason that these are important is that IGF-1 is a growth factor that's produced by many cells, but in the brain, it's produced by two of the major cell types in the brain, the neurons and the glial cells. And IGF-1 has a significant role in brain development as well as in recovery from injury and inflammation.

And it's thought that trofinetide, as I mentioned, it mimics a portion of IGF-1 or the GPE portion of it. It's thought that trofinetide works through this IGF-1 mechanism and that as a result, you get a decrease in inflammation of the brain, something called neuroinflammation. But it also is thought to help support synaptic function, which if you didn't take neuroscience you may not know what synaptic function means. But if you think about it, all these cells in our brain have to connect and communicate. That's how I'm able to talk to you right now. That's how I'm able to move my hands is that there's communication between those cells at those synapses. And trofinetide is thought to stimulate synaptic maturation and overcome some of the changes that happen as a result of the loss of MECP2. So changes that happen to neurons that have Rett Syndrome at the synapses, trofinetide is thought to help overcome some of those differences.

(TF) That's encouraging. And technical, but encouraging to hear that there's that process of rebuilding or developing new synapses. So that, you know, and it sounds like based on the fact that Rett Syndrome is so unique for each person that the way synapses will be redeveloped or grown will be different for each person. Everybody will see a little different effect. Let's talk a little bit more about the clinical trial process for trofinetide. We can talk a little bit historically, but let's specifically talk about phase three, the most recent study. What can you tell us about that?

(DP) So it has really been a long road to get to where we are. And I want to first highlight that NNZ-2566, which was the name of the compound before we called it trofinetide, first came to Rett Syndrome in a clinical trial in 2013. So it's been a decade since the first clinical trial was enrolling with NNZ-2566 for Rett Syndrome. So at that time in 2013, there was a phase two study that looked at the safety of trofinetide in adult women with Rett Syndrome aged 16 to 45. Then they moved on to another phase two study or safety study in kids with Rett Syndrome ages five to 15, these were all girls. And then with the result of these that were encouraging, in late 2019, a phase three clinical trial that was called LAVENDER Study began enrolling girls and women aged five to 20 with Rett Syndrome.

And so this was really the critical study, and it was the data from this study that the FDA used to evaluate the risk-benefit ratio of trofinetide. And so this was a study that was used to demonstrate that trofinetide had a benefit. So a little bit about the study, they enrolled over 180 participants, half of whom took trofinetide and the other half received a placebo.

And I want to pause here and say thank you to the hundreds of families that have participated in these clinical trials over the last decade. Because if we didn't have you as active research participants, as partners in this, we wouldn't be celebrating this today. So as I mentioned, half of those families agreed to, you know, well half the families, their daughter received a placebo the other half received trofinetide. And over the two-year study period, they evaluated how well did this work, using two different instruments, one that was completed by the caregiver and one that was completed by the doctor.

(TF) Thanks for sharing that. Yeah, and those families that participate in those early studies, you know, not to mention the most recent study, we're hearing some of the from them now of just how excited they are, how emotional it is to know that something they participated with their child years ago is paying off now. And so again, just to echo the gratitude for all of us who are benefiting as a community because of the sacrifice, the blood, sweat and tears that our community put into this over the last 10 years is huge.

Dominique, what were some of the results from the trofinetide study in this most recent LAVENDER study?

(DP) So as I mentioned in a clinical trial before you start the study, you have to say, what are the tools that we're gonna use to show that there is benefit? And so the two tools that were selected for this study were the Rett Syndrome Behavioral Questionnaire that the caregivers, it's a questionnaire that the caregivers complete. And then a clinical global impression of improvement scale that the study doctor would complete.

So we'll talk really about the Rett Syndrome behavioral questionnaire or sometimes called the RSBQ because that I think is what's most relevant for sharing with our families. So families would complete this RSBQ during each of their many study visits. And this RSBQ is a 45-item questionnaire that looks at eight major areas. So I'm gonna list off those areas to just give you a sense of what were they evaluating with this RSBQ. So those areas are general mood, breathing problems, hand behaviors, repetitive face movements, body rocking and expressionless face, nighttime behaviors, fear and anxiety, and walking and standing. So there are questions that fall into one of these eight. And when they evaluate the results for the entire group that was treated, every single one of those eight areas had improvement compared to the group of people that didn't get trofinetide, they took that placebo.

And so being able to have this comparison, you say, okay, well there was this, you know, half the group didn't get treatment and there was not a change in this RSBQ and the other half had a change in the side of improving. And because these two groups had everything else the same in the sense that they came to the doctor as often, they had blood drawn as often, they had clinical exams as often. So all those other factors were the same and the difference was the trofinetide. And that is what you do in clinical studies to demonstrate that it was as a result of a treatment that you got the improvements.

And I do wanna touch on, you know, when when we talk about these eight areas, it was not that any one person in the study got improvement in all eight areas, but when you look at the entire group that had trofinetide, all eight areas saw improvement. And that is, to me, pretty reassuring. It says that trofinetide is not a drug that's specifically and only will work on, say, breathing problems, because in fact there was also improvement in hand behavior and in walking and standing. And so again, the effect of the drug will be variable, it'll be different from person to person but it has the potential to see improvement in any of these eight areas for those that do get improvement from the drug.

(TF) I think that's really helpful to qualify for our community, thank you, Dominique. Just the eight areas of improvement, but also just the fact that it's going to vary from person to person on the drug I think is huge. There were some side effects. Can you talk a little bit about the side effects that people saw that were on the study and what that means?

(DP) The most common side effect that was reported was diarrhea. And in fact, about 80% of the people that were in the study experienced diarrhea. I'm sorry, 80% of the people that were taking trofinetide experienced diarrhea versus a much smaller percentage of the people that were taking the placebo formula. So diarrhea seems to be a side effect of trofinetide. And once they recognized this, Acadia worked with the doctors at the clinics to develop a plan to help manage the diarrhea. And so then they were able to implement that during the study so that when individuals started experiencing the diarrhea, they could implement this plan. And then about half of the individuals needed continued management for the diarrhea, and the other half of that 80% did not need continued management of the diarrhea. So diarrhea is definitely one that is well documented. There was also a report of vomiting with trofinetide and those were kind of the two biggest side effects that were noted.

(TF) Thank you. And then this was a 12-week, LAVENDER was a 12-week study that kind of, and you said that they saw improvements across those eight areas of the RSBQ But then there was an extension of that study called LILAC. Can you talk a little bit about that, and what Acadia has seen? While the FDA didn't review that information for the approval, those results have come out since. Can you talk a little bit about that?

(DP) Yes, I think that the results of the LILAC study are, you know, should be really quite encouraging to our community. As you mentioned, that first clinical trial, the LAVENDER study was only 12 weeks. And so the FDA could only look at what happened in those 12 weeks. After the participants completed their 12-week study, where again, half of them got placebo, and half of them had trofinetide, all of those participants had the opportunity to enroll in the LILAC study, which is an open-label, meaning everyone gets trofinetide. So there is no more placebo group. So everyone gets trofinetide, everyone knows they're on trofinetide and the doctors know their participant is on trofinetide because they're in this open-label extension. They continued the open-label extension, and recently Acadia showed results from 40 weeks of being in this open-label extension study. And what they saw is that the improvement in the RSBQ continued. So that suggests that it wasn't a plateau. So it wasn't that you saw improvement at 12 weeks and then nothing else changed, but there continued to be progress even, you know, through a 40-week time period. So I think this is encouraging where, you know, it might take time to see results for trofinetide for any one individual that decides to take it, but that there's a potential for kind of a long-term, you know, continued change as a result of trofinetide.

(TF) It's absolutely encouraging. Thank you for sharing that. Let's talk a little bit about DAYBUE. So that's what trofinetide is now called in the market as the FDA approved it. It has a new name that Acadia will be marketing in the US as DAYBUE. Who is it approved for? What was the label? And let's talk a little bit more about that.

(DP) I think the first thing to make sure everyone is aware of is that this is approved in the United States. And so as you mentioned, the FDA, the US Food and Drug Administration was the regulatory body that approved this. So right now it's approved in the United States. One of the most exciting parts of this approval was what was put in the label. So the label is where they describe what that approval is. And this is indicated for individuals with Rett Syndrome ages two and above, period. So what does this mean? How do we interpret this? This means girls, boys, women, and men with Rett Syndrome ages two on, there is no upper age limit.

(TF) This is huge. Such a huge--

(DP) It's huge! And for our boys and men with Rett Syndrome to have the opportunity to be included. This has been an understudied population because so much less has been known about our boys and men with Rett Syndrome. But they have the opportunity to access trofinetide.

(TF) That's so encouraging. Yeah, our community has been on pins and needles wondering who's actually going to get to benefit from this. So this was really one of the best-case scenarios that we could have received from the FDA. So absolutely huge. How is DAYBUE going to be administered? Like what kind of medicine is it?

(DP) So DAYBUE is a liquid. And so you will give it to your loved one with Rett Syndrome the same way you give other liquids. So if your loved one takes things by mouth or orally, then they can take it by mouth. If they have a G-tube, it can also be given by G-tube. So this will be administered like any other liquid that they consume.

(TF) Thanks. And then talk about the prescription process. Will they need a prescription for this drug?

(DP) Yeah, so this will be a prescription medication, and so their doctor will give a prescription. And what Acadia has done, because this will be delivered, you won't be able to go to your local pharmacy where you maybe get your other medications from. And this will be from what's called a specialty pharmacy. And so Acadia has set up a support system called Acadia Connect to really help in this time where you are getting that first prescription through, maybe trying to get insurance approval, and making sure that you are getting your medication from the specialty pharmacy as smoothly as can be with this prescription.

(TF) I think that's really encouraging. So as we shared at the beginning, we encourage you to speak to your doctor directly. Acadia's website for the medication DAYBUE is daybue.com - D-A-Y-B-U-E.com - and on the website, you can find information about the label that Dominique was sharing. You'll also see some FAQ information. That's going to be where you want to share that information with your doctor and talk to them about a treatment for your child or a loved one with Rett Syndrome. Anything else, Dominique, that you want to share about just DAYBUE as a whole, about what's next for treatments? What else do you want to share with our community?

(DP) First I do want to mention, you mentioned the daybue.com website. There's also a section of it that is for healthcare providers, and it would be helpful for you to share with your doctor that website so they can learn about the process so that they can help support you and your family in getting that prescription for DAYBUE, if that is something that you and your doctor decide is right for your loved one.

But really, I do want to touch on the fact that while we are celebrating this tremendous moment today, and we deserve to be celebrating this, because of the decade-plus of work that has gone into this, the millions of dollars, the hundreds of families that have contributed from wanting to enroll and not being able to, to enrolling, to financially helping to support, to just emotionally being supportive to being on the sidelines but waiting, you know, there's been so much that has gone into this.

But this is really just the tip of the iceberg for Rett Syndrome. What this has done for our community is it has demonstrated in a much bigger sense that Rett Syndrome is a therapeutic area that can successfully get to approved treatments. And what that really means is that companies who each have to decide the risk-benefit ratio for their investments say this is a therapeutic area with less risk because they have a defined way to bring a treatment all the way through to approval. This means they have the doctor

network, they have those tools that I talked about to show that there's benefit, and they have a community that's willing to participate in that clinical trial. So all of that is in place, which de-risks this for other companies. I mean, and we've seen this with one other rare disease called Spinal Muscular Atrophy or SMA, where they had an approval of a drug, and that first approval was tremendous for their community and it made the landscape such that other companies were willing to invest. They now have three approved treatments for SMA, which is a neurodegenerative disorder. One of those treatments is a gene therapy.

So this is a monumental moment, it is worth celebrating. We have to, you know, be here today and celebrate where we've come, but also know that this really is going to be opening up a world for us where we will hopefully continue to see, and we at IRSF are gonna push really hard to continue to develop more therapeutics, to get us more options, really so that all individuals with Rett Syndrome have treatments. We want to have as many as we can so that if a treatment doesn't work for one person, they have another option to try.

(TF) Absolutely, yeah, thank you, Dominique. That's really encouraging. And it is, it's just the beginning. We've blown the door open and you know, we've changed. We're continuing, this is changing the landscape for Rett Syndrome. You know, 40 years ago no one had even heard of Rett Syndrome, barely heard of Rett Syndrome. All this work has been done to bring research, to bring investments, to bring industry to this place. And now to have this and like, it's super exciting.

So thank you for sharing so much today, and I hope, I think it's beneficial and encouraging to our community. Thank you guys for watching and being a part of this. As we mentioned, please be sure to visit daybue.com for more information and to register. Acadia's going to be hosting an upcoming webinar specifically for the caregivers, and that's on March 28th. So we encourage you to register for that webinar and join Acadia as a part of that as they're sharing more information.

We also continue to encourage you to talk to your doctor, as we shared, about getting the information to them. There's a healthcare provider portion on daybue.com as Dominique mentioned.

And we also just want to encourage you, on our website, on the trofinetide page that we put out, there's a part where you can share your experience, your thoughts on this. Whether you are a part of the clinical trial or you just have emotions that are running high about this news, we want to hear from you and hear what gives you hope. So you can visit us, you can email us at treatment@rettsyndrome.org or you can use a form on our website at rettsyndrome.org/trofinetide-contact.

We'll be back very soon with a second video with our CEO Melissa Kennedy who will be sharing about what you can do now to advocate for affordable care and access to treatments like DAYBUE. So thanks for being part of this today.

(DP) Thank you.